REMARKS

As recommended by the Examiner, the priority date of the present Patent Application was corrected to September 9, 1998 (Application 60/099,643) wherein specific teachings for use of mature FLINT proteins in treating liver disease can be found e.g., on page 42.

The subject invention discloses novel methods of treating an individual suffering from various liver disorders. The novelty of the invention stems, in part, from the Applicant's discovery that the mature form of human FLINT proteins (e.g., SEQ ID NO: 6 and 8) bind FasL with at least the same affinity as the Fas receptor itself thereby disrupting the FasL – Fas receptor interaction. The present invention exploits this and other discoveries by providing the discovery that mature human FLINT polypeptides positively impact various liver disease states.

Claim Rejection – 35 U.S.C. § 103(a)

Claims 40-43 stand rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent Application Publication 2002/0065210 in view of Nagata *et al.* Science, 267 (1449-1456), 1995, as discussed by the Examiner in the Office Action mailed December 1, 2003 (Paper Number 34). Reconsideration is requested.

The Examiner argues that a person of ordinary skill in the art at the time the invention was made, and with reasonable expectation of success, would have been motivated to "employ a polypeptide having an amino acid sequence 100% identical to SEQ ID NO: 6 so as to inhibit Fas-mediated apoptosis, as taught by the 2002/0065210 publication, and to do so to treat individuals suffering from disorders of the liver...and in particular Fas-mediated apoptosis as taught by Nagata et al." Applicants respectfully traverse this rejection.

The PTO bears the burden of establishing a case of prima facie obviousness. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988). In order to establish a prima facie case of obviousness, it is necessary for the examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, that one having ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the *claimed invention*. See e.g., Carella v. Starlight Archery, 804 F.2d 135 (Fed. Cir. 1986). This suggestion cannot stem from the applicant's own disclosure, however. In re Ehrreich, 590 F.2d 902 (CCPA 1979).

The references cited by the Examiner, even in combination, do not teach or suggest the invention as claimed. Specifically, the cited references do not teach or suggest Applicants' mFLINT polypeptide with the amino acid sequence as shown in SEQ ID NO. 6 and SEQ ID NO. 8 as claimed.

Patent Application Publication 2002/0065210 ("'210"), cited by the Examiner, teaches the full length FLINT molecule which they refer to as "DcR3 polypeptide" (see paragraph 0045) and as "native sequence DcR3 ... a mature or full-length native sequence DcR3 comprising amino acids 1 to 300 of FIG.1 (SEQ ID NO:1)" (see paragraph 0047). In numerous locations throughout the '210 specification and claims, the DcR3 polypeptide is said to comprise amino acid residues 1 to 300 of FIG. 1, or amino acid residues 1 to 215 of FIG. 1, or amino acid residues 1 to X, wherein X is any one of the amino acid residues of 215 to 300 of FIG. 1. The '210 application does not teach the presence or even the possibility of an amino terminal truncated form of DcR3 and certainly does not teach nor recognize the importance of a molecule spanning specifically from amino acids 30-300 of what they identify as their SEQ ID NO:1, nor do they teach or suggest an activity for a molecule spanning specifically from amino acids 30-300 of their SEQ ID NO: 1.

The Applicants' invention discloses the ability of mature FLINT with a sequence as shown in SEQ ID NO:6 or SEQ ID NO: 8 to disrupt the FasL-Fas receptor interaction and modify apoptosis as well as the method of treating various liver disorders with a protein having the sequence of SEQ ID NO:6 or 8. Applicants' SEQ ID NO: 6 is amino acids 30-300 of the '210 application's SEQ ID NO: 1. Applicants' SEQ ID NO: 8 is nearly identical to SEQ ID NO: 6 but has an alanine instead of a glycine at residue 214 of the mature FLINT polypeptide. Before the disclosure of the present invention, it would not have been expected that the proteins with a sequence as shown in SEQ ID NO: 6 and SEQ ID NO: 8 of the present application would have the ability to bind FasL, to disrupt the FasL-Fas receptor interaction, to inhibit apoptosis, nor that such protein would be useful for treating various liver disorders and dramatically improving the survival rate of test animals in which inflammation and liver failure have been induced (See Example 18).

Conclusion

In view of the above amendments and remarks, it is respectfully submitted that all pending claims are in condition for allowance and early notification to that effect is

requested. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at (317) 655-9326.

Respectfully submitted,

MaryAnn Wiskerchen
Agent for Applicants
Registration No. 45,511
Phone: 317-655-9326

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

March 5, 2004